



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

The effects of halothane and isoflurane on cardiovascular function in laterally recumbent horses

Citation for published version:

Raisis, AL, Blissitt, K, Henley, W, Rogers, K, Adams, V & Young, LE 2005, 'The effects of halothane and isoflurane on cardiovascular function in laterally recumbent horses', *British Journal of Anaesthesia*, vol. 95, no. 3, pp. 317-325. <https://doi.org/10.1093/bja/aei180>

Digital Object Identifier (DOI):

[10.1093/bja/aei180](https://doi.org/10.1093/bja/aei180)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Early version, also known as pre-print

Published In:

British Journal of Anaesthesia

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



The effects of halothane and isoflurane on cardiovascular function in laterally recumbent horses

A. L. Rasis¹, K. J. Blissitt², W. Henley³, K. Rogers³, V. Adams³ and L. E. Young¹

¹ Department of Equine Clinical Studies and ³ Department of Veterinary Epidemiology, Animal Health Trust, Lanwades Park, Newmarket, Suffolk, UK. ² Department of Veterinary Clinical Studies, Royal (Dick) School of Veterinary Studies, Easter Bush Veterinary Centre, Near Roslin, Midlothian, UK

Key words: anaesthetics, volatile, halothane anaesthetics, volatile, isoflurane cardiovascular system, responses equipment, TOE model, horse veterinary anaesthesia.

Abstract

Background. Experimental studies in adult horses have shown that general anaesthesia maintained with isoflurane is associated with less depression of cardiovascular function compared with halothane anaesthesia. Adverse effects of intermittent positive-pressure ventilation (IPPV) have also been demonstrated. Nevertheless, the haemodynamic effects of these agents and the effects of differing modes of ventilation have not been assessed during clinical anaesthesia in horses undergoing surgery.

Methods. The haemodynamic effects of isoflurane or halothane anaesthesia during spontaneous or IPPV were studied non-invasively in 32 laterally recumbent horses undergoing elective surgery. Indices of cardiac function and measurements of femoral arterial blood flow and resistance were recorded using transoesophageal and transcutaneous Doppler echocardiography, respectively. Arterial pressure was measured directly using a facial artery catheter.

Results. Cardiac index (CI) was significantly higher during isoflurane anaesthesia than during halothane anaesthesia and was also higher during spontaneous ventilation with isoflurane. CI decreased significantly over time and an inverse relationship was observed between CI and mean arterial pressure (MAP). Horses with higher MAP had a significantly lower CI. During isoflurane anaesthesia, femoral arterial blood flow was significantly higher in both pelvic limbs compared with halothane anaesthesia, and flow in the lower limb was significantly higher during spontaneous ventilation than during IPPV. No significant change in femoral blood flow was observed over time.

Conclusion. The effects of anaesthetics and mode of ventilation on cardiovascular function recorded under surgical conditions in horses are similar to those reported under experimental conditions. However, in contrast with previous experimental studies, CI progressively decreased over time regardless of agent used or mode of ventilation employed.

Introduction

Recent data using prospective cohort studies have confirmed much higher perioperative mortality and morbidity associated with anaesthesia in horses¹ compared with humans² and with dogs and cats.³ Johnston and colleagues¹ reported that after emergency laparotomy cases were excluded from their dataset, the mortality rate associated with general anaesthesia in horses was 0.9%. As a result, there has been extensive research into the effects of different anaesthetics on equine cardiovascular function and their contribution to perioperative deaths. The effects of halothane and isoflurane anaesthesia on central and peripheral haemodynamics have been extensively studied in the laboratory, where both agents are observed to produce dose dependent decreases in cardiac function.^{4,5} However, at constant arterial carbon dioxide tension (P_{aCO_2}) halothane produces a greater depression of cardiac function than occurs during isoflurane anaesthesia.⁴ This was thought to result from greater depression of myocardial contractility by halothane than by isoflurane.⁶ Femoral arterial blood flow is higher during isoflurane anaesthesia than during halothane anaesthesia in horses not undergoing surgery,⁷ a finding consistent with indirect evidence that skeletal muscle blood flow is also higher during isoflurane anaesthesia. Significant temporal improvements in cardiac output and stroke volume have been observed during halothane and isoflurane anaesthesia.^{8,9} There is also experimental evidence that the effects of these agents differ during different modes of ventilation. During intermittent positive-pressure ventilation (IPPV) cardiovascular depression is significantly less during isoflurane anaesthesia than during halothane anaesthesia, although the effects of each agent on cardiovascular function did not differ significantly during spontaneous ventilation.⁴ It seems likely that depression of myocardial contractility by halothane is offset during spontaneous ventilation by increased sympathetic nervous system activity, secondary to increased P_{aCO_2} . Alternatively, or

additionally, cardiac output during spontaneous ventilation is maintained because there is less reduction of venous return.

The invasive nature of techniques used to measure cardiac function and skeletal muscle blood flow has prevented the study of the effects of different anaesthetics and mode of ventilation in clinical equine subjects undergoing surgical procedures; it is possible that the depressant effects of low inspired concentrations of halothane may be partially overcome by surgical stimulation.⁵ The recent development of non-invasive techniques, including transoesophageal¹⁰ and transcutaneous Doppler ultrasound,^{11,12} currently allows measurement of cardiac function and peripheral blood flow in clinical subjects. The purpose of this study was to use these techniques to determine the effects of different inhalational agents and mode of ventilation on cardiac function and femoral arterial blood flow in laterally recumbent horses undergoing anaesthesia for surgery.

Methods

Horses

Laterally recumbent horses undergoing orthopaedic and soft tissue surgery were studied. Horses undergoing procedures involving significant blood or fluid loss were excluded. First, the inhalational agent used for maintaining anaesthesia was randomly selected and then the mode of ventilation was randomly selected for each agent. Consequently, horses were randomly assigned to one of four groups: halothane and IPPV, halothane and spontaneous ventilation, isoflurane and IPPV or isoflurane and spontaneous ventilation (Table 1).

Anaesthesia

Food but not water was withheld for 12–18 h before anaesthesia. A jugular venous catheter was placed before induction of anaesthesia for i.v. drug administration. Horses were sedated

with romifidine 0.1 mg kg^{-1} i.v. and 5 min later anaesthesia was induced using ketamine 2.2 mg kg^{-1} and diazepam 0.05 mg kg^{-1} i.v. After orotracheal intubation, the horses were hoisted and positioned in lateral recumbency on a padded operating table and the endotracheal tube was connected to a circle breathing system. The selected inhalational agent was delivered in 50% nitrous oxide and 50% oxygen for the first 10 min and thereafter in 100% oxygen. The lungs of horses selected to receive IPPV were ventilated at 6–8 bpm with a tidal volume of $10\text{--}15 \text{ ml kg}^{-1}$ and an inspiratory:expiratory ratio of 1:3 using a large animal ventilator (Large Animal Anaesthesia Control Centre, North American Drager, Telford, USA). Ventilation was adjusted to maintain normocapnia (P_{aCO_2} 5.3–6.6 kPa). For horses assigned to spontaneous ventilation, IPPV was initiated if P_{aCO_2} exceeded 10.0 kPa during anaesthesia; the remaining data for these horses were excluded from subsequent analysis.

Horses were positioned on the operating table with the upper and lower limbs parallel and the lower thoracic limb pulled cranial to the upper limb. Approximately 5 min after connection to the anaesthetic machine, flunixin 1.1 mg kg^{-1} and morphine 0.12 mg kg^{-1} were administered intravenously. Isotonic polyionic fluids were administered via the jugular catheter at $10 \text{ ml kg}^{-1} \text{ h}^{-1}$.

Monitoring

Heart rate was monitored using a base-apex electrocardiograph. Arterial pressure was measured using a fluid-filled transducer connected to a catheter in the facial artery. The transducer was calibrated at 0 and 100 mm Hg using a mercury manometer and zeroed at the level of the manubrium sternae. The electrocardiograph and arterial pressure trace were displayed continuously throughout anaesthesia on an oscilloscope (Datex, Shelton Technical, Milton Keynes, Buckinghamshire, UK). End-tidal concentration of the inhalational agent used to maintain anaesthesia was measured using a piezoelectric agent monitor (Lamtec 605

pneu PAC Ltd, Luton, Bedfordshire, UK). Arterial blood was collected from the facial arterial catheter using a heparinized syringe for P_{aCO_2} , P_{aO_2} and pH measurement.

Cardiac function

Indices of left ventricular systolic function; left ventricular pre-ejection period (PEP), ejection time (ET) and left ventricular velocity time integral (VTI), were measured from the aortic velocity waveforms recorded using transoesophageal echocardiography (TOE).^{10,13} These indices were measured during anaesthesia after each sample time using the methods described by Young and colleagues.¹¹ Cardiac output (Qt) was calculated from the product of the aortic VTI, the cross-sectional area of the aorta and heart rate.¹³ The cross-sectional area of the aorta was calculated from its diameter measured above the sinus of Valsalva using the leading-edge method.¹³ The diameter was measured three times from each of three sequential cardiac systoles and the average taken. A sequence of five consecutive velocity waveforms was measured, timed to correspond to a single cycle of ventilation. CI was then calculated using the following formula:

$$CI = Qt / BSA \text{ (litre min}^{-1} \text{ m}^{-2}\text{)}$$

Where BSA is the body surface area and is given by¹⁴

$$BSA = 10.5 \times (\text{body mass [g]}^{2/3} \times 10^{-4} \text{ (m}^2\text{)})$$

The corrected ejection time (ETc) was calculated according to the formula¹⁵

$$ETc = ET / (\sqrt{\text{RR interval}}) \text{ (s)}$$

where RR interval was an average measurement made from the simultaneously derived base apex electrocardiograph. The RR intervals corresponding to the five cardiac cycles used to derive ET were measured.

Femoral blood flow and resistance

Femoral blood flow and indices of femoral vascular resistance (pulsatility index [PI] and end-diastolic deceleration slope [EDSS]) were measured using Doppler ultrasonography as previously described.¹² The diameter of the femoral arteries was measured from the outer edge of the proximal vessel wall to the inner edge of the distal vessel wall. The time-averaged mean velocity for the entire cycle (TAV), the volumetric flow, EDDS and PI were calculated from the arterial velocity waveforms. Average measurements recorded from six consecutive cardiac cycles were calculated.

Data collection

Data collection began once the horse had been positioned, ~20 min after connection to the breathing system. Aortic velocity waveforms, systolic, diastolic and mean arterial pressure, ventilatory frequency, tidal volume, inspiratory pressure and end-tidal concentration of inhalational agent were recorded every 10 min. Arterial blood gas and femoral arterial flow variables were recorded every 20 min.

Data analysis

The mean and standard deviation of cardiac function measurements and peripheral blood flow were calculated for each group. End-tidal concentrations of inhalation agent used to maintain anaesthesia were expressed as a percentage of MAC of each agent in horses (0.88 and 1.31 for halothane and isoflurane, respectively¹⁶). Statistical analyses were conducted to assess the effects of anaesthetic agent and mode of ventilation on selected measurements of cardiovascular function including CI, PEP, ET, ETc, MAP, lower femoral arterial blood flow (LAF), upper femoral arterial blood flow (UAF), difference in flow (measured by LAF–UAF)

and indices of femoral vascular resistance (EDDS and PI). The measurements LAF and UAF were indexed to the mass of the horse with the formula used to calculate CI.

Associations between the cardiovascular measures, the anaesthetic and the mode of ventilation were assessed using linear mixed-effects models fitted using the maximum likelihood estimation.¹⁷ Correlations between successive measurements on the same horse were modelled using parametric models for covariance structure in longitudinal data.¹⁸ Akaike's Information Content (AIC) values¹⁹ were used to compare models with compound symmetry (random intercepts) and first-order autoregressive covariance structures. The mixed-effects models were built using a forward selection approach. Fixed effects were included in the models if they were significantly associated with outcome (Wald $P < 0.05$). Adjustments were made for heart rate and arterial blood gas tensions (P_{aCO_2} and P_{aO_2}) by including them as covariates in the mixed-effect models (when statistically significant). Biologically meaningful two-way interaction terms were tested between the main effect variables. Contrasts were used to conduct customized hypothesis tests on combinations of model parameters (e.g. effect of mode of ventilation for horses during halothane anaesthesia). Diagnostic plots were used to check the model fit against the raw data; fitted mean response profiles were superimposed on a time plot of the average observed response within each covariate–time combination, and the fitted variogram was superimposed on a plot of the empirical variogram.¹⁸

To assess the effect of blood pressure on cardiac function and femoral blood flow, MAP was added as an explanatory variable to the mixed-effects models for CI, LAF and UAF. Other fixed effects in the model were then eliminated by backward selection. A similar procedure was used to assess the relationship between cardiac output and femoral blood flow.

Results

The characteristics (mean [standard deviation]) of the horses in each group are presented in Table 1. Descriptive statistics (mean [standard deviation]) of the measurements of the central and peripheral cardiovascular function of the horses in each group recorded at 20, 40, 60, 80, 100 and 120 min are presented in Tables 2–5. Each group consisted of eight horses. Incomplete data resulted from failure to position the TOE transducer, failure of the TOE probe temperature sensor, differences in the duration of anaesthesia as dictated by the surgery and the need to institute IPPV in horses developing hypercapnia (Tables 2–5).

Effects of agent and mode of ventilation on cardiovascular function

CI during isoflurane anaesthesia was significantly higher than that during halothane anaesthesia ($P<0.001$). Mode of ventilation also had a significant effect on CI. Spontaneous ventilation was associated with a higher CI than IPPV during isoflurane anaesthesia ($P=0.01$), but this effect was not observed during halothane anaesthesia ($P=0.99$). A model with linear and quadratic effects for time revealed a significant decrease in CI over time with the rate of decrease being steeper after 60 min ($P=0.02$ for quadratic effect). There was no association between CI and either P_{aCO_2} or P_{aO_2} after adjustment for anaesthetic and ventilation ($P=0.9$ and $P=0.6$, respectively). The final multivariable mixed-effects model for CI is shown in Table 6. Diagnostic plots confirmed that the model provided a satisfactory fit to the data (see Fig. 1 for the fitted and observed mean response profiles).

Pre-ejection period during halothane anaesthesia was significantly higher than that during isoflurane anaesthesia after adjusting for heart rate ($P<0.001$) but was not significantly associated with mode of ventilation ($P=0.2$), P_{aCO_2} ($P=0.2$) or P_{aO_2} ($P=0.1$). Pre-ejection period increased linearly with time ($P<0.001$).

Conversely, corrected ejection time during isoflurane anaesthesia was significantly higher than that during halothane anaesthesia ($P<0.001$) and was also significantly higher during spontaneous ventilation than during IPPV ($P=0.03$). ETc decreased during surgery ($P=0.01$ for quadratic effect); however, P_{aCO_2} and P_{aO_2} were not significant in this model ($P=0.6$ and $P=0.5$, respectively).

In contrast with other measurements of central cardiovascular function, there were no significant associations between MAP and anaesthetic ($P=0.3$) or mode of ventilation ($P=0.4$). The relationship between MAP and time was modelled using a quadratic function (linear effect -0.339 , $P=0.005$, and quadratic effect 0.002 , $P=0.001$). This demonstrated that MAP initially decreased with time, reaching a minimum at 80 min before increasing slightly during the latter part of surgery (but without returning to initial values). Mean arterial pressure was not significantly associated with P_{aCO_2} ($P=0.2$) or P_{aO_2} ($P=0.8$).

Femoral arterial blood flow recorded in the lower limb (LAF) was significantly higher during isoflurane anaesthesia than during halothane anaesthesia ($P=0.003$). Mode of ventilation was also observed to have a significant effect on LAF. Horses breathing spontaneously had a significantly higher LAF than horses receiving IPPV ($P=0.03$). This effect was no longer significant after adjustment for P_{aCO_2} ($P=0.2$). Femoral arterial blood flow recorded in the upper limb (UAF) during isoflurane anaesthesia was also significantly higher than that recorded during halothane anaesthesia ($P<0.001$), but UAF was not significantly associated with mode of ventilation ($P=0.8$). Femoral arterial flow in the lower and upper limb did not vary significantly over time ($P=0.4$ and $P=0.8$, respectively).

Femoral flow in the lower limb and P_{aO_2} were associated ($P=0.001$), but femoral flow in the upper limb was not associated with P_{aO_2} ($P=0.5$). Adjustment for P_{aO_2} in the model for lower limb femoral flow increased the magnitude of the effect for mode of ventilation.

Neither measure of femoral resistance (lower arterial pulsatility index and upper arterial pulsatility index) was associated with agent ($P=0.1$ and $P=0.06$, respectively), mode of ventilation ($P=0.8$ and $P=0.08$, respectively) or time ($P=0.4$ and $P=0.3$, respectively) before and after adjustment for P_{aO_2} or P_{aCO_2} .

Assessment of differences between femoral arterial blood flow in the lower and upper limbs revealed that, on average, horses had significantly higher levels of flow in the lower limb compared with the upper limb ($P<0.001$). Assessment of the effects of mode of ventilation on this difference revealed a significantly greater difference between flow in the lower and upper limbs in spontaneously breathing horses compared with horses receiving IPPV ($P<0.001$), although this effect was no longer significant after adjustment for P_{aCO_2} ($P=0.2$). No associations were found between differences in lower and upper femoral arterial blood flow with anaesthetic ($P=0.2$) or time ($P=0.4$). Arterial partial pressure of oxygen was associated with the differences in blood flow between the upper and lower femoral arteries ($P=0.003$) and adjustment for P_{aO_2} in the mixed-effects model increased the estimated effect of the mode of ventilation.

Relationship between indices of cardiovascular function

When corrected ejection time was included in the model that explored the effects of agent and ventilation on CI, ETc was the only significant variable retained in the model ($P<0.001$). Similarly, when CI was included in the model that explored the effects of agent and ventilation on ETc, cardiac index ($P<0.001$) and agent ($P=0.009$) were the only significant variables retained in the model.

After adjusting for agent, mode of ventilation, P_{aCO_2} , P_{aO_2} , time and correlation between measurements on the same horse, it was observed that horses with higher MAP had lower Qt. A mean increase in MAP of 10 mm Hg was significantly associated with a mean drop in Qt

of $1.8 \text{ litre min}^{-1}$ (95% confidence interval [CI], -2.7 to -0.9). There was also a positive relationship between MAP and femoral arterial flow, although a stronger but negative relationship was found between femoral arterial flow and indices of femoral vascular resistance. Ignoring femoral resistance, a mean increase in MAP of 10 mm Hg was associated with a mean increase in LAF of 63 ml min^{-1} (95% CI, 14–111) and a mean increase in UAF of 51 ml min^{-1} (95% CI, 19–84) after adjustment for covariates. After inclusion of PI in models relating LAF and UAF to MAP, the effect of MAP became non-significant and a strong negative relationship between PI and femoral arterial flow became apparent. Mean increases of 1 unit in lower and upper limb PI were associated with mean decreases in lower and upper limb femoral flow of 23 ml min^{-1} (95% CI, 13–33) and 16 ml min^{-1} (95% CI, 11–20), respectively. In contrast, no significant associations were observed between Qt and LAF, UAF, LAPl or UAPl (*P*-values of 0.8, 0.3, 0.08 and 0.07 respectively).

Discussion

The use of transoesophageal echocardiography and peripheral vascular ultrasonography allowed the cardiovascular effects of two commonly used inhalational agents, isoflurane and halothane, to be studied in equine clinical cases undergoing soft tissue and orthopaedic surgery.

Comparison of the cardiovascular effects of the two inhalational agents revealed that isoflurane was associated with significantly greater CI and ETc and significantly reduced PEP compared with halothane. Ejection time and PEP are heart-rate-dependent indices of cardiac function influenced by preload, afterload and myocardial contractility.²⁰ In humans, ETc has a clinically useful relationship with left ventricular filling pressure, as assessed by pulmonary arterial wedge pressure,^{21,22} and has been used as a non-invasive estimate of left ventricular preload.^{23,24} The fact that ETc was significantly higher in horses anaesthetized by

isoflurane, regardless of the mode of ventilation employed, suggests that differences in CI between the two agents are related to differing effects on cardiac preload. However, in common with other ejection phase indices of left ventricular function, ETc is also influenced by myocardial contractility and afterload when these influences are not controlled.²² Therefore, as has been suggested previously,^{4,7} higher CI in horses anaesthetized with isoflurane could also reflect better myocardial contractility and lower systemic vascular resistance compared with horses anaesthetized with halothane.

In humans, changes in preload can also be estimated from changes in the volume of the left ventricle at end diastole measured from two-dimensional ultrasound images obtained from a transoesophageal transducer. These images could not be obtained in this study because of the large size of the horses and the different anatomical relationship between the oesophagus and cardiac axis in quadrupeds. At the maximum imaging depth of the equipment (24 cm), only the ascending aorta and pulmonary artery could be visualized to the level of the valve leaflets and unfortunately repeatable standardized images of the left atrium could not be obtained.

Femoral arterial blood flow was also significantly higher during isoflurane anaesthesia in this and other studies.⁷ It has been suggested that beneficial effects of isoflurane on limb blood flow arise because it reduces systemic vascular resistance.⁶ However, the inhalational agent had no significant effect on PI, the Doppler index of femoral resistance used in the current study, and so this hypothesis fails to explain the improved femoral arterial flow during isoflurane anaesthesia under clinical conditions in horses. We were also unable to demonstrate any association between Qt and femoral arterial blood flow from our data.

These data also showed that cardiac output and ETc tended to be higher during spontaneous ventilation than during IPPV, although the difference in CI only attained statistical significance in horses anaesthetized with isoflurane. VTI, an index closely related to stroke volume,^{25,26} was higher in this group. These findings are consistent with results of previous

experimental work in which reduced cardiac function during IPPV was attributed to the detrimental effect of positive intrathoracic pressure on venous return and cardiac preload.⁴

Femoral arterial blood flow in the lower limb was greater in horses that breathed spontaneously than in horses receiving IPPV, regardless of agent used. In contrast, there was no significant effect of mode of ventilation or inhalational agent on flow in the upper limb. Increased arterial flow in the lower limb compared with the upper limb has been reported previously in horses^{7,27} and was attributed to hydrostatic pressure effects reducing flow in the upper pelvic limb.^{28,29} The difference in blood flow between upper and lower limbs was greater in spontaneously breathing horses than in horses receiving IPPV, regardless of agent used. The higher LAF in horses breathing spontaneously was associated with P_{aCO_2} . P_{aO_2} was associated with differences in flow between the upper and lower pelvic limbs. Local effects of carbon dioxide and oxygen on vascular tone may have contributed to increased flow in the lower limb, whilst similar effects on vascular tone in the upper pelvic limb might have been modulated by the opposing influence of hydrostatic pressure. However, no association was found between PI and ventilation to support this hypothesis. Increased intrathoracic pressure reduces Qt by reducing venous return and augments intrathoracic arterial pressure, thereby increasing perfusion pressure.³⁰ As a result, the net effect of IPPV on MAP and peripheral blood flow depends on the balance between these opposing effects.³⁰

Changes in cardiovascular function over time also occurred. CI and ETc decreased progressively over the course of anaesthesia, and within each group there was an initial decrease in MAP followed by a slight increase after 80 min. The initial decrease in MAP may have resulted from the additive depressant effects of the sedative and induction agents on cardiovascular function, which are likely to diminish over time. The subsequent increases in MAP are consistent with other experimental studies,^{5,8} although previous workers have reported simultaneous increases in cardiac output.^{8,31} The decrease in CI over time in the

present study may have resulted from the cardiovascular effects of sympathetic nervous system activation in response to surgery, leading to peripheral vasoconstriction and increased left ventricular afterload.^{32,33} This possibility is supported by the presence of an inverse relationship between MAP and CI in all groups. However, the latter findings may also have resulted from progressive decreases in contractility and preload, a hypothesis that is supported by concurrent reductions in ETc and increases in left ventricular PEP over time in the current study, regardless of agent used.

In horses anaesthetized with halothane, there were marked decreases in ETc and reciprocal increases in PEP. In some horses PEP exceeded ET in the latter stages of anaesthesia. This finding could reflect greater depression of ventricular contractility with halothane and the inability of compromised ventricles to overcome increased afterload caused by sympathetic nervous system activation. Alternatively, or additionally, halothane administration to these horses may have been associated with greater pooling or redistribution of blood volume resulting in failure to maintain normal cardiac preload and thence cardiac output. Progressive decreases in cardiac output over time during surgical anaesthesia may contribute to the increased risk of perioperative morbidity and mortality associated with increasing duration of anaesthesia.¹ No significant association was observed between femoral arterial blood flow and CI, although there was a significant positive relationship with MAP and a strong negative relationship between PI and femoral arterial flow. This finding supports our previous experimental study in which marked decreases in femoral arterial blood flow and concurrent increases in femoral vascular resistance occurred in anaesthetized horses after vasoconstrictor drugs were given.¹¹

We have demonstrated differences in central and peripheral haemodynamic function in laterally recumbent horses, dependent upon mode of ventilation, P_{aCO_2} , P_{aO_2} and inhalational agent used. Despite this, none of the horses developed postoperative complications, such as

postanaesthetic myopathy. As a result, the study cannot be used to support the use of one anaesthetic over another. Further clinical studies are required in larger numbers of horses undergoing longer operations to ascertain whether clinically relevant differences in the effects of these agents become apparent.

This study was limited by the loss of data resulting when surgery ended before 120 min (dropouts) and intermittent missing values that resulted from technical problems with the transoesophageal transducer. It may be reasonable to assume, as was done in these analyses, that the mechanism generating intermittent missing values was completely random, but the mechanism responsible for dropouts may have been 'informative'.³⁴ This is potentially important, as treating informative dropouts as random may introduce bias into the parameter estimates.

In conclusion, this study showed that many of the differences in cardiovascular function between halothane and isoflurane anaesthesia under controlled experimental conditions also occur during surgical anaesthesia in horses. However, in contrast with previous experimental studies, CI and Qt declined progressively with time regardless of agent used or mode of ventilation employed. Furthermore, this study provides further evidence that IPPV has detrimental effects on cardiac function in laterally recumbent anaesthetized horses.

Acknowledgments

This study was supported by a project grant from the Home of Rest for Horses.

References

- Johnston GM, Eastment JK, Wood JLN, Taylor PM. The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of phases 1 and 2. *Vet Anaesth Analg* 2002; 29: 159–70
- Lunn JN, Mushin WW. Mortality associated with anaesthesia. *Anaesthesia* 1982; 37: 856
- Dyson DH, Maxie MG. Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. *J Anim Hosp Ass* 1998; 35: 325–35
- Steffey EP, Howland D Jr. Comparison of circulatory and respiratory effects of isoflurane and halothane anesthesia in horses. *Am J Vet Res* 1980; 41: 821–5
- Steffey EP, Howland D Jr. Cardiovascular effects of halothane in the horse. *Am J Vet Res* 1978; 39: 611–15
- Brunson DB. Use of halothane and isoflurane in the horse. *Vet Clin North Am Equine Pract* 1990; 6: 529–41
- Raisis AL, Young LE, Blissitt KJ et al. A comparison of the haemodynamic effects of isoflurane and halothane anaesthesia in horses. *Equine Vet J* 32: 318–26
- Dunlop CI, Steffey EP, Miller MF, Woliner MJ. Temporal effects of halothane and isoflurane in laterally recumbent ventilated male horses. *Am J Vet Res* 1987; 48: 1250–5
- Steffey EP, Hodgson DS, Dunlop CI et al. Cardiopulmonary function during 5 h of constant-dose isoflurane in laterally recumbent, spontaneously breathing horses. *J Vet Pharmacol Ther* 1987; 10: 290–7

- Young LE, Blissitt KJ, Clutton RE, Molony V, Darke PGG. Feasibility of transoesophageal echocardiography for evaluation of left ventricular performance in anaesthetised horses. *Equine Vet J* 1996; 19: 63–70
- Rasis AL, Young LE, Meire HB, Taylor PM, Blissitt KJ, Marlin D et al. Measurements of hindlimb blood flow recorded using Doppler ultrasound during administration of vasoactive agents in halothane-anesthetized horses. *Vet Radiol Ultrasound* 2000; 41: 64–72
- Rasis AL, Young LE, Meire H, Walsh K, Taylor PM, Lekeux P. Repeatability of Doppler ultrasound measurements of hindlimb blood flow in halothane anaesthetised horses. *Equine Vet J* 2000; 32: 239–46
- Young LE, Blissitt KJ, Bartram DH, Clutton RE, Molony V, Jones RS. Measurement of cardiac output by transoesophageal Doppler echocardiography in anaesthetized horses: comparison with thermodilution. *Br J Anaesth* 1996; 77: 773–80
- Veenman JN, Dujardint CL, Hoek A, Grootendorst A, Klein WR, Rutten VP. High volume continuous venovenous haemofiltration (HV-CVVH) in an equine endotoxaemic shock model. *Equine Vet J* 2002; 34: 516–22
- Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. *Crit Care Med* 1991; 19: 1132–7
- Steffey EP, Howland D Jr, Giri S, Eger EI. Enflurane, halothane, and isoflurane potency in horses. *Am J Vet Res* 1977; 38: 1037–9
- Searle SR, Casella G, McCulloch CE. *Variance Components*. New York: John Wiley, 1992.
- Diggle PJ, Liang K-Y, Zeger SL. *Analysis of Longitudinal Data*. Oxford: Clarendon Press, 1994.

- Akaike H. New look at the statistical model identification. IEEE Trans Autom Control 1974; 19: 716–23.
- Borow KM. An integrated approach to the noninvasive assessment of left ventricular systolic and diastolic performance. In: St. John Sutton M, Oldershaw PJ, eds. Textbook of Adult and Paediatric Echocardiography and Doppler. Boston: Blackwell, 1989; 97–168
- DiCorte CJ, Latham P, Greilich PE, Cooley MV, Grayburn PA, Jessen ME. Esophageal Doppler monitor determinations of cardiac output and preload during cardiac operations. Ann Thorac Surg 2000; 69: 1782–6
- Singer M, Allen MJ, Webb AR, Bennett ED. Effects of alterations in left ventricular filling, contractility, and systemic vascular resistance on the ascending aortic blood velocity waveform of normal subjects. Crit Care Med 1991; 19: 1138–45
- Madan AK, UyBarreta VV, Aliabadi-Wahle S et al. Esophageal Doppler ultrasound monitor versus pulmonary artery catheter in the hemodynamic management of critically ill surgical patients. J Trauma 1999; 46: 607–11
- Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. Crit Care Med 1991; 19: 1132–7
- Bennett ED, Barclay SA, Davis AL, Mannering D, Mehte N. Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. Cardiovasc Res 1984; 18: 632–8
- Wallmeyer K, Wann S, Sagar KB, Kalbfleisch J, Kloppfenstein HS. The influence of preload and heart rate on Doppler echocardiographic indexes of left ventricular performance: comparison with invasive indexes in an experimental preparation. Circulation 1986; 74: 181–6

- Branson KR, Benson GJ, Thurmon JC, Olson WO, Tranquilli WJ, Dorner JL. Haemodynamic parameters and tissue oxygenation during halothane anesthesia in normal horses and those experiencing post operative lameness. *J Equine Vet Sci* 1992; 12: 153–9
- Seymour RS, Hargens AR, Pedley TJ. The heart works against gravity. *Am J Physiol* 1993; 265: R715–20
- Peters P, Baker SR, Leopold PW, Taub NA, Burnand KG. Compartment syndrome following prolonged pelvic surgery. *Br J Surg* 1994; 81: 1128–31
- Berne RM, Levy MN. Control of cardiac output: coupling of the heart and blood vessels. In Schmidt WR, Dowell RE, eds. *Cardiovascular Physiology*. St Louis: Mosby, 2001; 199–225
- Steffey EP, Dunlop CI, Cullen LK et al. Circulatory and respiratory responses of spontaneously breathing, laterally recumbent horses to 12 h of halothane anesthesia. *Am J Vet Res* 1993; 54: 929–36
- Taylor PM, Kirby JJ, Shrimpton DJ, Johnson CB. Cardiovascular effects of surgical castration during anaesthesia maintained with halothane or infusion of detomidine, ketamine and guaifenesin in ponies. *Equine Vet J* 1998; 30: 304–9
- Wagner AE, Dunlop CI, Heath RB, Turner AS, Trotter GW. Hemodynamic function during neurectomy in halothane-anesthetized horses with or without constant dose detomidine infusion. *Vet Surg* 1992; 21: 248–55
- Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. New York: John Wiley, 1987.

Legends

Tab.1

Characteristics of the horses and surgical procedures. Data are presented as mean (range) for age, or mean (SD)

Tab.2

Descriptive statistics [mean (SD)] for measurements of central cardiovascular function recorded in horses anaesthetized with halothane. *Data missing due to transoesophageal echocardiography probe temperature sensor fault. † Data missing due to failure to position transoesophageal echocardiography probe. ‡ Data missing due to completion of surgical procedure

Tab.3

Descriptive statistics [mean (SD)] for measurements of peripheral cardiovascular function recorded in horses anaesthetized with halothane. *Data missing because of completion of surgical procedure.

Tab.4

Descriptive statistics [mean (SD)] for measurements of central cardiovascular function recorded in horses anaesthetized with isoflurane. *Data missing because of a temperature sensor fault in the TOE probe. † Data missing because of completion of surgical procedure. ‡ Data missing because of exclusion of horses with $\text{PaCO}_2 > 75 \text{ mm Hg}$, and thence given IPPV

Tab.5

Descriptive statistics [mean (SD)] for measurements of peripheral cardiovascular function recorded in horses anaesthetized with isoflurane. *Data missing because of completion of surgical procedure. † Data missing because of exclusion of horses with $\text{PaCO}_2 > 75 \text{ mm Hg}$, and hence given IPPV

Tab.6

Final multivariable mixed-effects model for cardiac index. *Wald P-values. † A first-order autoregressive process was chosen for the covariance structure reflecting a constant correlation between successive CI measurements on the same horse and an exponential decrease in correlation as the time interval between measurements increased. (The lower AIC=1830 for the autoregressive model suggests a better fit to the data compared with the value of 1916 for a model with compound symmetry covariance)

Fig.1

Cardiac index (CI) of horses undergoing surgery split by anaesthetic agent and mode of ventilation: observed and fitted mean response profiles. The drop in the mean CI profile for the spontaneous isoflurane group at times >70 min is due to the termination of surgery for all but one horse in this group.

Tab.1

Group	Age (yr)	Body mass (kg)	Gender	Type of surgery	Duration (min)
Halothane: IPPV	10.5 (5–16)	566 (51.9)	Geldings n=6 Females n=2	Soft tissue n=5 Orthopaedic n=3	120 (75.0)
Halothane: spontaneous	8.75 (5–14)	563 (54.6)	Geldings n=8 Females n=0	Soft tissue n=5 Orthopaedic n=3	92.5 (41.0)
Isoflurane: IPPV	8.38 (6–12)	561 (68.5)	Geldings n=5 Females n=3	Soft tissue n=3 Orthopaedic n=5	155 (97.2)
Isoflurane: spontaneous	6.75 (4–11)	574 (151.7)	Geldings n=6 Females n=2	Soft tissue n=5 Orthopaedic n=3	77.5 (21.9)

IPPV, intermittent positive-pressure ventilation.

Tab.2

Mechanically ventilated						
Time (min)	20	40	60	80	100	120
Horses (n)	3*†	6*	6*	4*†	4*†	1*†
MAC (%)	1.10 (0.13)	1.10 (0.15)	1.13 (0.14)	1.26 (0.21)	1.23 (0.10)	1.30 (-)
MAP (mm Hg)	83 (10)	84 (9)	82 (11)	76 (12)	72 (12)	68 (8)
SAP (mm Hg)	115 (9)	113 (9)	114 (23)	98 (13)	98 (12)	93 (10)
DAP (mm Hg)	71 (10)	72 (12)	70 (12)	65 (12)	60 (10)	53 (3)
CI (litre min ⁻¹ m ⁻²)	4.6 (1.4)	3.9 (0.9)	3.4 (0.9)	3.0 (0.6)	2.8 (1.0)	2.2 (-)
VTI (m s ⁻¹)	21 (2)	18 (4)	16 (5)	13 (4)	12 (5)	7 (-)
HR (beats min ⁻¹)	35 (6)	34 (5)	35 (3)	36 (4)	36 (3)	38 (-)
PEP (s)	0.22 (0.03)	0.23 (0.03)	0.26 (0.02)	0.29 (0.04)	0.30 (0.06)	0.30 (-)
ETc	0.36 (0.03)	0.31 (0.04)	0.29 (0.06)	0.24 (0.07)	0.27 (0.07)	0.21 (-)
PaCO ₂ (mm Hg)	47 (7)	47 (6)	46 (6)	44 (2)	42 (2)	47 (-)
PaO ₂ (mm Hg)	329 (76)	388 (77)	405 (110)	444 (49)	427 (52)	410 (-)
pH	7.40 (0.04)	7.42 (0.04)	7.43 (0.03)	7.44 (0.04)	7.45 (0.05)	7.41 (-)

Spontaneously ventilated						
Time (min)	20	40	60	80	100	120
Horses (n)	6*†	7*	4*	3*‡	2*‡	2*‡
MAC (%)	1.30 (0.20)	1.10 (0.11)	1.20 (0.12)	1.10 (0.17)	1.40 (0)	1.40 (0)
MAP (mm Hg)	87 (15)	82 (9)	78 (11)	76 (6)	74 (11)	70 (6)
SAP (mm Hg)	116 (14)	107 (10)	101 (12)	103 (4)	98 (13)	94 (14)
DAP (mm Hg)	70 (14)	67 (9)	64 (10)	65 (9)	73 (2)	61 (7)
CI (litre min ⁻¹ m ⁻²)	3.6 (0.3)	4.2 (0.8)	3.3 (1.1)	2.5 (0.5)	2.0 (0.7)	1.8 (0.5)
VTI (m s ⁻¹)	20 (2)	22 (4)	19 (6)	16 (5)	11 (3)	9 (2)
HR (beats min ⁻¹)	32 (5)	32 (3)	32 (6)	31 (2)	32 (2)	32 (3)
PEP (s)	0.23 (0.03)	0.22 (0.04)	0.26 (0.09)	0.32 (0.07)	0.37 (0.06)	0.37 (0.04)
ETc	0.32 (0.02)	0.34 (0.03)	0.31 (0.06)	0.25 (0.02)	0.23 (0.02)	0.22 (0.02)
PaCO ₂ (mm Hg)	66 (5)	63 (6)	63 (9)	70 (6)	62 (1)	62 (7)
PaO ₂ (mm Hg)	235 (116)	279 (112)	282 (125)	167 (63)	157 (87)	148 (87)
pH	7.31 (0.03)	7.33 (0.03)	7.34 (0.04)	7.29 (0.03)	7.33 (0.01)	7.34 (0.04)

MAC, minimum alveolar concentration; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CI, cardiac index; VTI, velocity time integral; HR, heart rate; PEP, pre-ejection period; ETc, corrected ejection time.

Tab.3

Mechanically ventilated

Time (min) Horses (<i>n</i>)	20 8	40 8	60 8	80 5*	100 4*	120 2*
UAF (ml min ⁻¹ m ⁻²)	96 (40)	100 (38)	90 (38)	74 (20)	62 (22)	25 (–)
TAV upper limb (m s ⁻¹)	7.7 (2.7)	7.9 (2.3)	6.9 (2.8)	5.9 (1.5)	5.5 (1.8)	2.0 (–)
EDDS upper limb (m s ⁻¹ s ⁻¹)	234 (46)	210 (49)	215 (26)	231 (54)	216 (36)	176 (–)
PI upper limb	13.0 (10.7)	10.5 (7.6)	12.0 (9.8)	10.4 (2.4)	15.2 (12.6)	7.5 (–)
LAF (ml min ⁻¹ m ⁻²)	107 (48)	131 (64)	121 (38)	100 (31)	74 (28)	60 (–)
TAV lower limb (m s ⁻¹)	9.6 (4.4)	10.9 (4.8)	9.7 (3.5)	8.4 (3.5)	6.3 (2.4)	4.5 (–)
EDDS lower limb (m s ⁻¹ s ⁻¹)	217 (74)	206 (79)	191 (48)	210 (59)	211 (80)	258 (–)
PI lower limb	9.5 (10.4)	11.1 (17.1)	6.6 (5.4)	7.4 (3.9)	9.5 (6.0)	11.8 (–)

Spontaneously ventilated

Time (min) Horses (<i>n</i>)	20 8	40 8	60 8	80 5*	100 4*	120 2*
UAF (ml min ⁻¹ m ⁻²)	100 (49)	95 (27)	87 (36)	60 (15)	70 (11)	53 (16)
TAV upper limb (m s ⁻¹)	8.1 (5.1)	7.4 (3.5)	7.1 (3.7)	4.5 (1.4)	4.3 (1.1)	3.3 (0.4)
EDDS upper limb (m s ⁻¹ s ⁻¹)	209 (53)	214 (71)	204 (43)	192 (30)	192 (18)	167 (66)
PI upper limb	10.6 (7.3)	11.1 (4.5)	19.2 (17.9)	21.9 (9.4)	11.4 (3.0)	24.8 (14.6)
LAF (ml min ⁻¹ m ⁻²)	152 (43)	178 (52)	180 (47)	118 (22)	81 (3)	53 (4)
TAV lower limb (m s ⁻¹)	12.1 (3.9)	13.9 (4.5)	15.1 (5.6)	9.3 (3.9)	6.2 (2.5)	4.5 (1.8)
EDDS lower limb (m s ⁻¹ s ⁻¹)	178 (36)	154 (20)	164 (28)	186 (40)	209 (37)	202 (3)
PI lower limb	4.5 (1.4)	4.0 (1.4)	4.1 (1.5)	8.3 (5.5)	7.8 (3.0)	13.2 (7.4)

UAF, upper hindlimb blood flow indexed to body surface area; LAF, lower hindlimb blood flow indexed to body surface area; EDDS, early diastolic deceleration slope; PI, pulsatility index; TAV, temporal averaged velocity.

Tab.4

Mechanically ventilated

Time (min) Horses (<i>n</i>)	20 8	40 8	60 8	80 5*	100 4*	120 2*
MAC (%)	1.0 (0.14)	0.93 (0.10)	0.96 (0.10)	1.00 (0.06)	1.00 (0.10)	1.05 (0.08)
MAP (mm Hg)	95 (16)	93 (24)	84 (16)	81 (18)	80 (19)	111 (25)
SAP (mm Hg)	129 (18)	119 (23)	112 (10)	111 (21)	110 (19)	133 (24)
DAP (mm Hg)	86 (21)	79 (19)	74 (21)	74 (14)	75 (16)	97 (18)
CI (litre min ⁻¹ m ⁻²)	5.3 (1.9)	5.1 (1.6)	5.3 (1.9)	4.8 (1.7)	4.6 (1.8)	3.7 (2.3)
VTI (m s ⁻¹)	24 (6)	23 (6)	24 (6)	22 (6)	21 (7)	16 (8)
HR (beats min ⁻¹)	33 (2)	34 (4)	36 (3)	35 (4)	35 (3)	34 (5)
PEP (s)	0.16 (0.03)	0.15 (0.03)	0.14 (0.03)	0.15 (0.04)	0.17 (0.06)	0.21 (0.08)
ETc	0.38 (0.04)	0.40 (0.05)	0.41 (0.04)	0.41 (0.05)	0.39 (0.06)	0.34 (0.04)
Pa _{CO₂} (mm Hg)	46 (5)	47 (4)	48 (3)	48 (5)	47 (6)	48 (5)
Pa _{O₂} (mm Hg)	296 (82)	325 (84)	365 (104)	376 (143)	303 (89)	295 (144)
pH	7.42 (0.04)	7.43 (0.02)	7.44 (0.02)	7.42 (0.03)	7.44 (0.04)	7.43 (0.04)

Spontaneously ventilated

Time (min) Horses (<i>n</i>)	20 8	40 6 [†]	60 5 [†]	80 1* [‡]
MAC (%)	0.97 (0.05)	1.02 (0.04)	1.08 (0.07)	1.10 (-)
MAP (mm Hg)	80 (4)	73 (6)	74 (17)	97 (-)
SAP (mm Hg)	107 (8)	100 (7)	98 (19)	114 (-)
DAP (mm Hg)	66 (6)	58 (5)	63 (17)	-
CI (litre min ⁻¹ m ⁻²)	7.2 (1.9)	7.2 (1.8)	6.2 (1.4)	3.7 (-)
VTI (m s ⁻¹)	31 (6)	33 (4)	30 (6)	20 (-)
HR (beats min ⁻¹)	37 (5)	38 (6)	37 (7)	29 (-)
PEP (s)	0.11 (0.01)	0.11 (0.02)	0.12 (0.02)	0.15 (-)
ETc	0.46 (0.03)	0.48 (0.03)	0.46 (0.04)	0.41 (-)
Pa _{CO₂} (mm Hg)	69 (11)	64 (6)	64 (10)	65 (-)
Pa _{O₂} (mm Hg)	208 (67)	233 (45)	233 (99)	166 (-)
pH	7.28 (0.06)	7.31 (0.05)	7.29 (0.03)	7.27 (-)

MAC, minimum alveolar concentration; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CI, cardiac index; VTI, velocity time integral; HR, heart rate; PEP, pre-ejection period; ETc, corrected ejection time.

Tab.5

Mechanically ventilated

Time (min) Horses (<i>n</i>)	20 8	40 8	60 8	80 5*	100 5*	120 4*
UAF (ml min ⁻¹ m ⁻²)	131 (34)	142 (34)	151 (56)	144 (63)	152 (76)	162 (46)
TAV upper limb (m s ⁻¹)	11.3 (3.6)	12.8 (3.7)	12.3 (4.5)	11.1 (4.9)	12.0 (6.3)	13.3 (5.8)
EDDS upper limb (m s ⁻¹ s ⁻¹)	155 (27)	160 (42)	154 (47)	135 (33)	138 (52)	114 (60)
PI upper limb	5.4 (1.5)	5.2 (1.9)	6.0 (3.6)	8.3 (9.4)	9.5 (13)	2.8 (0.7)
LAF (ml min ⁻¹ m ⁻²)	148 (39)	164 (37)	167 (35)	176 (46)	161 (94)	221 (76)
TAV lower limb (m s ⁻¹)	13.1 (3.2)	14.9 (4.1)	14.4 (2.8)	14.2 (3.2)	15.7 (4.7)	16.7 (7.8)
EDDS lower limb (m s ⁻¹ s ⁻¹)	132 (23)	129 (25)	124 (35)	130 (27)	102 (24)	91 (19)
PI lower limb	3.9 (1.2)	3.5 (1.0)	3.7 (1.7)	3.8 (2.4)	2.7 (1.3)	2.1 (0.5)

Spontaneously ventilated

Time (min) Horses (<i>n</i>)	20 8	40 6 [†]	60 5 [†]	80 1* [†]
UAF (ml min ⁻¹ m ⁻²)	143 (37)	132 (29)	152 (30)	214 (–)
TAV upper limb (m s ⁻¹)	11.6 (5.2)	10.4 (3.6)	11.4 (4.1)	13.4 (–)
EDDS upper limb (m s ⁻¹ s ⁻¹)	210 (73)	190 (51)	164 (52)	155 (–)
PI upper limb	11.4 (8.3)	12.0 (7.7)	10.2 (7.4)	5.5 (–)
LAF (ml min ⁻¹ m ⁻²)	185 (38)	182 (20)	202 (57)	286 (–)
TAV lower limb (m s ⁻¹)	15.6 (4.0)	15.5 (4.9)	14.9 (4.2)	18.3 (–)
EDDS lower limb (m s ⁻¹ s ⁻¹)	163 (24)	164 (44)	150 (66)	119 (–)
PI lower limb	5.1 (2.3)	5.5 (3.1)	5.3 (3.5)	3.0 (–)

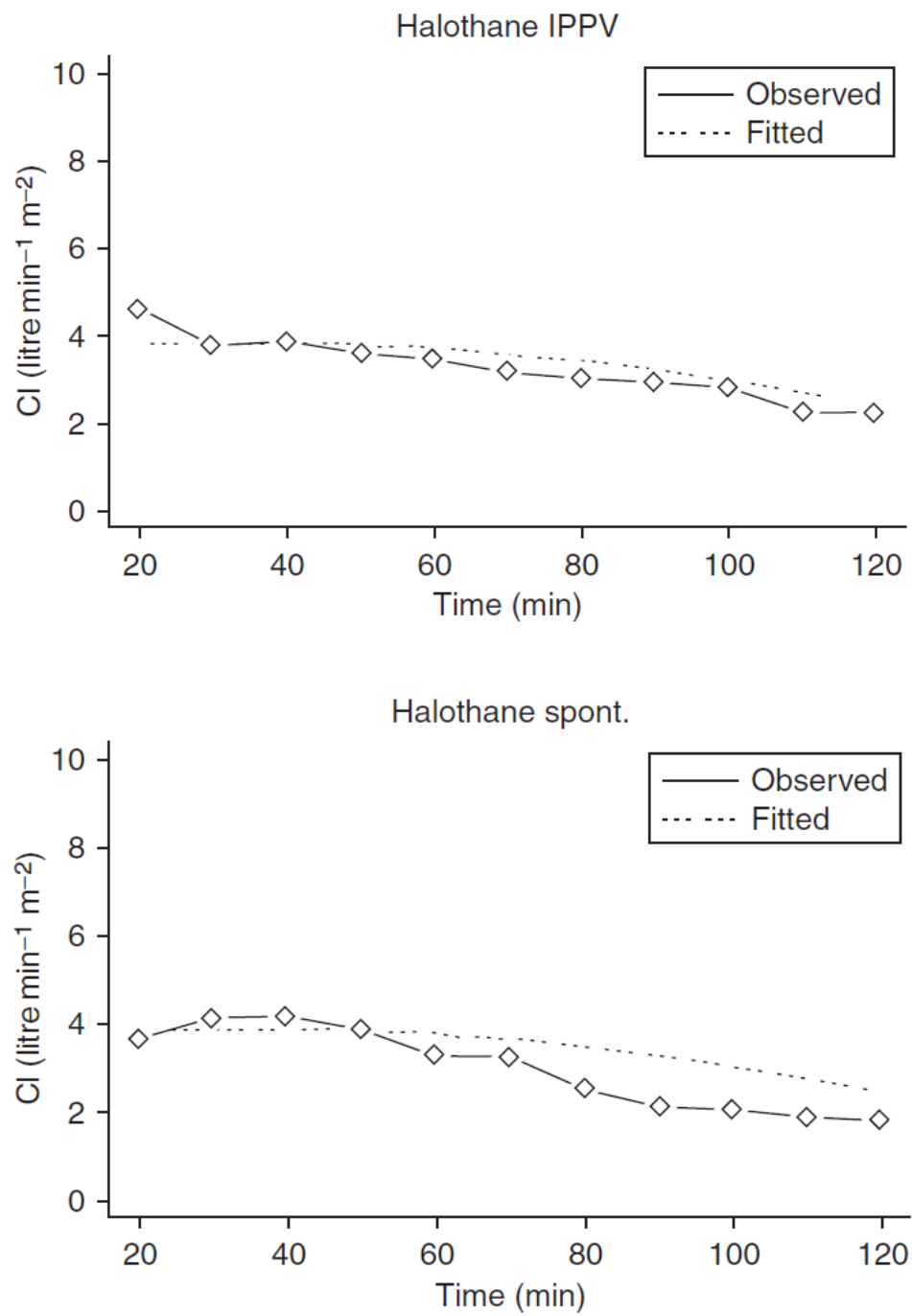
UAF, upper hindlimb blood flow indexed to body surface area; LAF, lower hindlimb blood flow indexed to body surface area; EDDS, early diastolic deceleration slope; PI, pulsatility index; TAV, temporal averaged velocity.

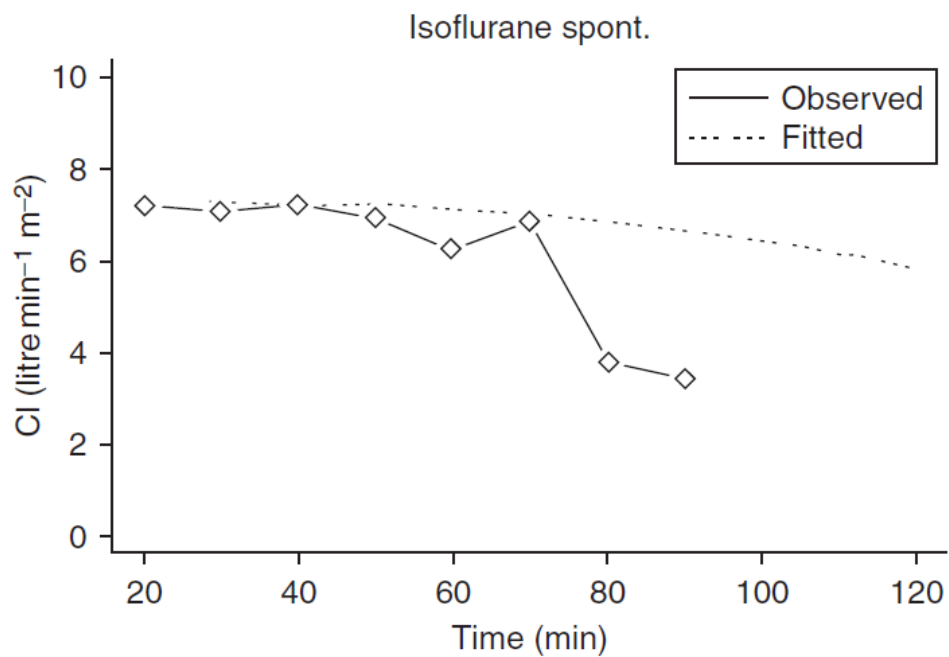
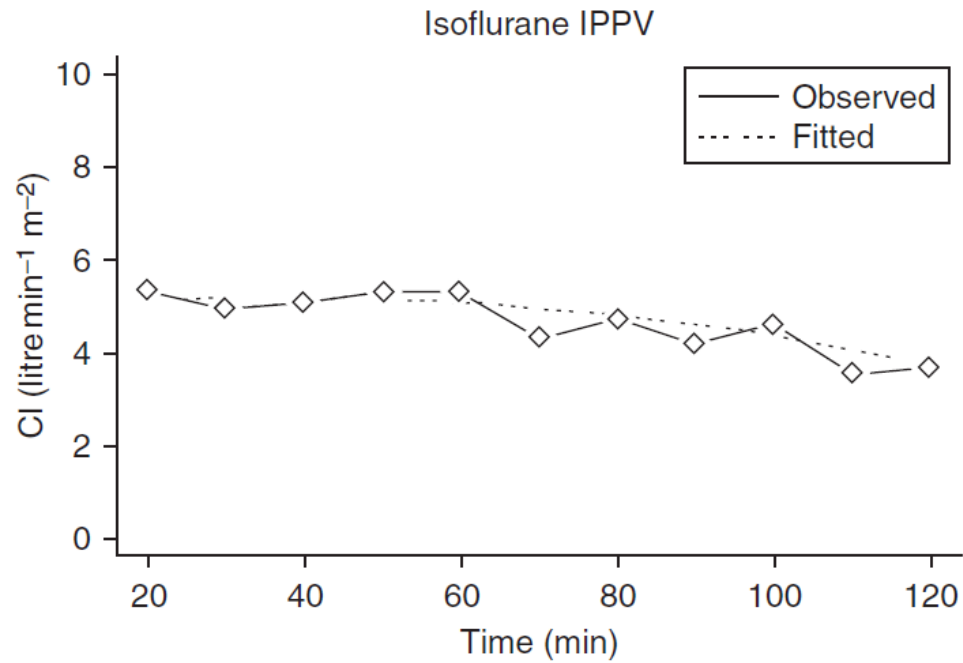
Tab.6

	Estimate	Standard error	<i>P</i> -value*
Fixed effects			
Intercept	6.9902	0.5647	<0.001
Time	0.0129	0.0107	0.229
Time [†]	−0.0002	0.0001	0.019
Agent			
Halothane	−3.3667	0.6725	<0.001
Isoflurane	Referent		
Ventilation			
IPPV	−2.0140	0.6891	0.008
Spontaneous	Referent		
Agent × ventilation			
Halothane × IPPV	1.9730	0.9434	0.049
Halothane × Spontaneous	Referent		
Isoflurane × IPPV	Referent		
Isoflurane × spontaneous	Referent		
Covariance parameters			
Autocorrelation [†]	0.9167	0.0209	<0.001
Residual variance	1.7226	0.3984	<0.001

IPPV, intermittent positive-pressure ventilation.

Fig.1





Cardiac index (CI) of horses undergoing surgery split by anaesthetic agent and mode of ventilation: observed and fitted mean response profiles. The drop in the mean CI profile for the spontaneous isoflurane group at times >70 min is due to the termination of surgery for all but one horse in this group.

